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EXPERIMENTS ON A METHOD OF PREVENTING
DEATH FROM SNAKE BITE, CAPABLE OF
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BY

SIR LAUDER BRUNTON, M.D., F.R.S.,
SIR JOSEPH FAYRER, BART., K.C.S.I., F.R.S.,
AND
LEONARD ROGERS, M.D., B.S.

"Experiments on a Method of Preventing Death from Snake Bite, capable of Common and Easy Practical Application." By Sir LAUDER BRUNTON, M.D., F.R.S., Sir JOSEPH FAYRER, Bart., K.C.S.I., F.R.S., and LEONARD ROGERS, M.D., B.S., etc., Indian Medical Service. Received February 22,—Read May 5, 1904.

Although this paper is a joint one, the authors wish to mention that each has had a different part in its production. The whole research may be fairly regarded as the natural outcome of the work begun in India nearly forty years ago by one of us (Fayrer), and this is the only ground on which his name can be associated with this paper. The instrument employed was designed by another of us (Brunton), and the actual experimental work was entirely carried out by a third (Rogers).

The first experiments on the use of permanganate of potash as an antidote to snake poison was made by one of us (Fayrer), in 1869, both by the local application of a solution and by injection into the veins,* on the ground of its being a chemical antidote. The animals experimented upon were dogs, but the permanganate of potash did not seem to have any power to avert the lethal action of the poison. It was shown also by Wynter Blyth† that Cobra venom when mixed *in vitro* with permanganate of potash becomes innocuous. His results were confirmed by two of us, who showed that some other substances had a similar power.‡ They tried by the injection of strong solution of permanganate of potash, and also by its local application to an incision made over the bite, to destroy the lethal action of Cobra poison previously injected, but their experiments were unsuccessful, the permanganate appearing to be unable to overtake the poison which had got the start of it.

In 1881 Messrs. Couty and Lacerda§ made a number of experiments upon the effect of permanganate of potash on serpents' venom, and Lacerda found that permanganate of potash not only destroyed the lethal action of the venom when mixed with it *in vitro*, but also preserved life when a 1-per-cent. solution of permanganate was injected into the tissues close to the place where the venom had been

* 'The Thanatophidia of India,' 1872, p. 95, by J. Fayrer, M.D., London, and A. Churchill.

† "The Poison of the Cobra," by A. Wynter Blyth, M.R.C.S., 'The Analyst,' February 28, 1877, p. 204.

‡ "Note on the Effect of Various Substances in Destroying the Activity of Cobra Poison," Brunton and Fayrer, 'Roy. Soc. Proc.,' June 20, 1878, vol. 27, 465.

§ Couty and Lacerda, 'Comptes Rendus,' vol. 92, p. 465.

previously injected, and also when both venom and antidote were injected directly into the vein. At the time of presenting his note to the Academy of Science in Paris, M. Lacerda was apparently unaware of the previous experiments by Blyth, Brunton and Fayerer. In a later publication* he discusses their experiments, but claims for himself to have scientifically demonstrated permanganate of potash to be a precious antidote to serpent venom, and to have brought it into common use, and thinks, therefore, that the priority belongs to him; but he was apparently unaware that instructions for its use with the ligature had many years before been promulgated by Fayerer in India.

In the winter of 1881 a number of experiments were made by Dr. Vincent Richards, who found, like the previous experimenters, that Cobra poison was completely destroyed by permanganate of potash when mixed with it *in vitro*, so that death did not follow the injection of the mixture either hypodermically or into a vein. He found also that when Cobra poison was injected into a dog, and the injection followed either immediately or after an interval of 4 minutes by a hypodermic injection into the same part of a solution of permanganate of potash no symptoms of Cobra poisoning resulted, but after the development of symptoms of Cobra poisoning permanganate of potash failed to have any effect whether injected locally or into a vein or both.

These results obtained both by Lacerda† and Richards seemed to give good hope that permanganate of potash might be used to lessen the appalling fatalities from snake bite in India, but it is evident that the hypodermic injection of a solution can never be widely employed because the hypodermic syringe is expensive, it is liable to get out of order just at the times that it is wanted and the solution may become dried or spilt or may not be available. It is evident that the first requisite for any antidote to snake poisoning is that it shall be always at hand; second, that it shall be easily applied; and thirdly, that it shall be cheap.

About two years ago one of us (Brunton) was asked on behalf of a young officer going out to India, to design an instrument which might be used in case of snake bite. He did so accordingly, and he has since had a similar one made for him by Messrs. Arnold and Sons which seems to combine the three requisites just noted. It consists of a lancet-shaped blade about half an inch long, long enough in fact to reach the deepest point of a bite by the largest snake. He has had some instruments made with a double edge like an ordinary lancet, and others with one edge sharp and the other edge blunt, so as to

* Lacerda, 'Comptes Rendus,' vol. 93, p. 466.

† "O Veneno ophidico e seus antidotos," Dr. J. B. do Lacerda, Rio de Janeiro, Lombaerts, &c., 1881, p. 64.

press in the permanganate. The lancet is set in a wooden handle about an inch and a half long, which is hollowed at the other end so as to form a receptacle to hold the permanganate. Two wooden caps are fitted over the ends of the instrument, one to keep in the permanganate, and the other to protect the lancet. Such an instrument, if turned out in large numbers, could be sold at such a small price as to be within reach of even the Indian labourer, and might be sold everywhere in the same way as packets of quinine are at present.

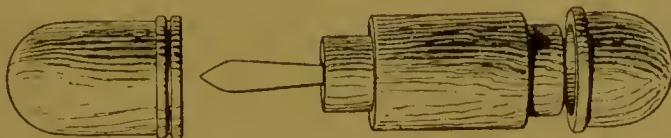


FIG. 1.—Lancet for use in snake bite, showing the steel blade, the cap which covers it, the hollow wooden handle for holding crystals of permanganate or potash, and the cover which retains them.

The plan now proposed is to make a free opening into the site of the bite, and to rub in crystals of permanganate. For this purpose the limb should be surrounded by a tight bandage above the bite, the puncture of the tooth or teeth should be freely cut into by the lance-shaped blade and the crystals of permanganate introduced and rubbed round. A few drops of saliva may be added.

To test the efficacy of the proposed plan several lethal doses of venom dissolved in a few drops of water, so as to resemble, as far as possible, the natural poison, are to be injected into the limb of an animal, a ligature placed round the limb above the seat of injection, an incision made, and crystals of permanganate placed in the wound, moistened and rubbed in.

Experimental Investigation, by Leonard Rogers.

In order to test in as practical a manner as possible the value of the suggestion of the two first-named authors of this communication, the following experiments were carried out at the Physiological Laboratory of the London University by the third-named author. In the first place it was necessary to ascertain if crystals of permanganate destroy the activity of other venoms besides that of the Cobra, for we are not aware that its action in this direction has been tested against any extensive series of snake venoms. As the value of the suggested treatment would evidently be greatly enhanced if the permanganate could be shown to act efficiently against every class of snake venom, a series of experiments were carried out to test this point. The venoms in solution were mixed with small quantities of

a 10-per-cent. solution of pure crystalline permanganate of potash in 0·9 per cent. NaCl, and after given times the mixtures were injected into pigeons, several times a lethal dose of each venom being used, so that if recovery took place it would be evident that the permanganate had destroyed the activity of the poisons. The following table (p. 327) summarises the results of these experiments.

It will be seen that the table includes venoms of each main subdivision of snakes, namely, the two true vipers, the *Daboia Russellii* of India and the Puff Adder of Africa, the Pit Viper, the *Crotalus horridus*, the Colubrine snake the *Bungarus fasciatus*, and one of the Hydrophidæ or Sea-snakes, namely, the *Enhydrina bengalensis*. In the case of each ten or more lethal doses were neutralised by very small quantities of permanganate in solution, and in most of them twenty lethal doses were readily thus rendered harmless. The only failure was in Experiment 7, in which 32·2 milligrammes of *Bungarus fasciatus* venom was added to 25 milligrammes of permanganate of potash in solution, and in this case by far the greater part of the poison must have been neutralised, for in previous experiments one-eighteenth part of the venom per kilogramme, used in Experiment 7, killed a pigeon in 1 hour. Further experiments showed that 25 milligrammes of the permanganate of potash did entirely neutralise 16·1 milligrammes of *Bungarus fasciatus* venom. It is evident then that the salt will neutralise about its own weight of this venom, but that its power in this direction has a definite limit as might have been expected. It is clear, then, that this agent does act on every class of snake venom and renders them inert.

Owing to the limited time available and the small number of animals for which a license had been obtained, the actual experiments on the treatment after injection of the venoms have been so far limited to those of the Cobra as a typical representative of the Colubrine class, and of the *Daboia Russellii* as a common and deadly viper. Rabbits and cats were used in the investigation, the latter on account of their mixed diet and firmer tissues resembling more closely the human subject. The venoms were dissolved in as small a quantity of sterile normal saline solution (0·9 per cent. NaCl) as possible, so as to resemble in concentration the natural venoms. The portion of the limb to be operated on was cleaned of hair by scissors beforehand (as the human subject is free from this obstacle to treatment). The strong solution of venom was then injected into the subcutaneous tissues of the cleaned part of a hind limb a little above the paw, as most snake bites in the human subject occur on the distal parts of the extremities. After a given measured time a ligature consisting of a piece of bandage was tied loosely round the thigh and twisted up tightly by means of a piece of stick or a pencil so as to temporarily stop the circulation through the distal part of the limb in order to

Table I.

| Number of experiment. | Weight of pigeon. | Dose in milligrammes. | Number of lethal doses. | Dose per kilogramme weight. | Amount of 10 per cent. K_2MnO_4 . | Time mixed before injection. | Symptoms. | Result. |
|-------------------------------------|-------------------|-----------------------|-------------------------|-----------------------------|-------------------------------------|------------------------------|-----------|------------------|
| I. Daboia Venom. | | | | | | | | |
| 1..... | 350 | 3.5 | 3 | milligrammes. | c.c. | mins. | Nil | Recovered. |
| 2..... | 320 | 6.2 | 7 | 10 | 0.5 | 30 | Do. | Do. |
| 3..... | 280 | 14 | 17 | 20 | 0.5 | 10 | Do. | Do. |
| 4..... | 300 | 15 | 10 | 50 | 0.5 | 10 | Do. | Do. |
| II. <i>Crotalus horridus</i> Venom. | | | | | | | | |
| 5..... | 270 | 21.6 | 20 | 80 | 0.25 | 5 | Do. | Do. |
| 6..... | 300 | 12 | 10 | 40 | 0.25 | 5 | Do. | Do. |
| III. African Puff Adder. | | | | | | | | |
| 7..... | 230 | 32.2 | 20 | 140 | 0.25 | 5 | Colubrine | Died in 2 hours. |
| 8..... | 230 | 16.1 | 10 | 70 | .. | 10 | Nil | Recovered. |
| 9..... | 250 | 25 | 20 | 0.25 | 10 | Do. | Do. | Do. |

check further absorption of the poison. An incision was then made in the long axis of the limb over the seat of injection of the poison, and the edges dissected up slightly on either side so as to fully expose the affected tissues and to form a small pocket, into which the crystals of permanganate were next placed, and after moistening with a few drops of sterile normal salt solution (water, or even saliva, would serve in an emergency) they were well rubbed in until the exposed tissues presented a uniformly blackened appearance. About 3 minutes were usually occupied by the little operation, on the completion of which the ligature was released and a dressing and bandage applied to the wound. The animals were under chloroform throughout the operation, including the injection of the venom. The amount of permanganate held by the instrument made for these experiments was $\frac{1}{4}$ gramme, this quantity being used in each of the experiments.

The results of the experiments so far performed may most conveniently be summarised in the following table, by means of which they may readily be studied. The actual doses of venoms injected are given in Column 4, and the dose per kilogramme weight in Column 5. The time which was allowed to elapse after the injection of the poison before the application of the ligature (Column 6) was usually $\frac{1}{2}$ minute, which it was calculated would be sufficient to allow a handkerchief, or in the case of a native a strip of a *pngari* or of the cotton garments commonly worn by the poorer classes in the tropics, being tied round the limb and twisted up to form an efficient ligature. In a few of the later experiments this application of the ligature was delayed for 5 and 10 minutes. In Column 8 the time is shown which was taken over the operation from the application to the release of the ligature, while the ultimate result is shown in Column 9. In most of the control experiments a ligature was applied round the thigh for about the same time as in the operations, as it appeared possible that the ligature might delay somewhat the absorption of the poison, although it could scarcely affect the ultimate result of its action, owing to the poison being an essentially cumulative one.

The first six experiments of Table II were performed on rabbits, with the result that only prolongation of life was obtained. Thus, after a dose of 10 milligrammes per kilogramme (Experiment 1), death took place only a little quicker than after one-tenth of this dose in a control animal (Experiment 5). Again 5 milligrammes per kilogramme in a treated animal caused death in $3\frac{1}{2}$ hours (Experiment 2), but 0.5 milligramme per kilogramme in a control killed in the same time (Experiment 6). The rapidity of death in this last animal shows that 0.5 milligramme per kilogramme is still much above the minimal lethal dose of *Cobra* venom for rabbits, so that the doses used in the treated cases were many times a lethal dose (about five to fifty times),

Table II.—Experiments with Cobra Venom.

| No. | Animal. | Weight. | Actual dose. | Dose per kilogramme. | Time of ligature. | Amount of permanganate. | Ligature released after. | Result. |
|-----|------------------|---------|--------------|----------------------|-------------------|-------------------------|--------------------------|------------------|
| 1 | Rabbit | 1 | 10 | milligrammes. | seconds. | grammes. | mins. | Died, 1 hr. |
| 2 | " | 1½ | 7·5 | 10 | 5 | 0·25 | 2½ | ," 3½ ,, |
| 3 | " | 1½ | 3·75 | 2½ | .. | .. | 3½ | ," 3½ ,, |
| 4 | " | 2¾ | 2·75 | 1 | .. | .. | 3 | ," 3½ ,, |
| 5 | " | 1·8 | 1·8 | 1 | .. | Nil (control) | .. | ," 1½ ,, |
| 6 | " | 2½ | 1·25 | 0·5 | 30 | .. | 3½ | ," 3½ ,, |
| 7 | Cat | 1¾ | 17·5 | 10 | .. | 0·25 | 3 | Recovered. |
| 8 | " | 3 | 30 | 10 | .. | Nil (control) | 3½ | Died, 3 hrs. |
| 9 | " | 3 | 15 | 5 | .. | 0·25 | 3 | Died, 30-38 hrs. |
| 10 | " | 2¾ | 13·75 | 5 | .. | .. | 3½ | Recovered. |
| 11 | " | 4 | 20 | 5 | 5 minutes | .. | 3½ | ," |
| 12 | " | 3 | 15 | 5 | .. | Nil (control) | 3 | Died, 28 hrs. |
| 13 | " | 3½ | 10·5 | 3 | 10 minutes | 0·25 | 3½ | Recovered. |
| 14 | " | 2 | 4 | 2 | 5 | .. | 3 | ," |
| 15 | " | 3½ | 3½ | 1 | .. | Nil (control) | .. | Died, 50 hrs. |

and were thus mostly proportionally larger doses than a Cobra could eject in the case of a man. The tissues of a rabbit are also more delicate than those of a cat or of a man, so that absorption of the poison may be unusually rapid in rabbits, which are extremely susceptible to snake venoms.

Turning next to the results of the experiments on cats, much more satisfactory results were obtained. Thus, the control experiments showed that 1 milligramme per kilogramme produced death in 50 hours, this being the minimal lethal dose of the Cobra venom used in these experiments for cats (Experiment 15). A dose of 5 milligrammes per kilogramme caused death in 28 hours, the time having probably been prolonged by the application of a ligature after the injection (Experiment 12). A dose of 10 milligrammes per kilogramme proved fatal in 3 hours, although a ligature had been applied as in the treated cases (Experiment 8). On comparing the result of treated cases with the above control we find only one death occurred in six experiments. The one fatal result took place after a dose of 5 milligrammes per kilogramme (Experiment 9), this having been the first case treated, in which the permanganate was not as thoroughly rubbed in, and the site of injection was not as completely exposed as in later experiments, and in this case death did not take place until over 30 hours. On the other hand, in Experiment 7 recovery took place after 10 milligrammes per kilogramme (ten lethal doses), while in two other cases recovery took place after five lethal doses had been injected, in one of which (Experiment 11) 5 minutes were allowed to elapse before the treatment was carried out, while in Experiment 13 recovery ensued from lethal doses treated 10 minutes after injection.

The above results are very encouraging, for it appears from D. D. Cunningham's observations that the average amount of venom ejected by a full-sized Cobra is not more than ten lethal doses for a man, while other writers give much smaller amounts. Further, in many cases, the full dose will not actually be injected into the human tissue for various reasons.

In Table III a similar series of experiments with *Daboia* venom are summarised. Here again, in the case of rabbits, only very marked prolongation of life was obtained, although the dose used in Experiment 17 was less than four lethal doses, so that it is clear that in the case of rabbits the method was not very successful.

On the other hand, the experiments with cats were as successful as in those of the Cobra series given above; for only one of the six cases treated with permanganate died, and in this instance (Experiment 21) the very large dose of 50 milligrammes per kilogramme was injected, and the treatment was delayed for 5 minutes. This dose is probably relatively larger than could be injected by any known viper in the case of a full-grown man. Further, in this case death did not take

place until upwards of 24 hours after the injection, while in a control experiment with the same dose (Experiment 22) a fatal result occurred in 4 hours. Further, with the same large dose recovery took place when treatment was carried out $\frac{1}{2}$ minute after injection. Again, 30 milligrammes per kilogramme (three lethal doses) killed a control cat in $4\frac{1}{2}$ hours, but in three cases treated $\frac{1}{2}$, 5 and 10 minutes respectively after injection all recovered, as did one after 10 milligrammes per kilogramme, although a control with this last dose died in 30—40 hours. In all the experiments of both series the recovered animals were alive and well 5 days and upwards after the injection of the venoms, which is 2 days longer than death has ever taken place in any of the control animals.

The above results are very encouraging, as the Viperine poisons are much less powerful, weight for weight, than are most of the Colubrines and Hydrophidæ, so that the amount of venom ejected by them can seldom, if ever, be more than two or three times a lethal dose for man.

In the course of the experiments it was observed that, even when the incision was made only 30 seconds after the injection of the poison into the subcutaneous tissues, a distinct blood-stained effusion is found, which serves as a very useful guide to the location and limits of the injected poison; after 5 or 10 minutes the effusion is more extensive, and in these cases the incisions were prolonged up the limb for about 2 inches in order to try and destroy as much of the venom as possible. The fact that as favourable results have been obtained after 5 minutes as after $\frac{1}{2}$ minute, may very possibly depend on the effusion noted materially checking the absorption of the poisons, so that at the end of that time the rate of absorption may become very much less rapid than during the first few seconds after its injection. That a very rapid absorption occurs during the first few seconds after the injection (probably on account of the action of the poison in preventing clotting of the blood locally) is certain, for it was shown by Fayerer many years ago that a dog bitten in the tail by a full-sized Cobra died in spite of the tail being cut off between the bitten part and the body a few seconds after the bite. In such cases, however, the dose received is relatively much larger than could be injected by a Cobra in the case of such a large animal as man, so that in practise (except in the very rare cases where the poison is injected directly into a vein) a fatal dose may not enter the system for some considerable time after the bite. This probability is supported by the fact that, in the case of Colubrine poisons at any rate, the minimal lethal dose is the same whether the venom is given subcutaneously or intravenously, yet it takes 1 or 2 days to produce death when injected under the skin, but only 5—20 minutes when inserted into a vein, so that under the former conditions the whole of the poison does not enter the circulation for a long period. These facts

Table III.—Experiments with *Daboia* Venom

| No. | Animal. | Weight. | Actual dose. | Dose per kilogramme. | Time of ligature. | Amount of permanganate. | Ligature released after. | Result. |
|-----|--------------|---------|----------------------|----------------------|-------------------|-------------------------|--------------------------|--------------------|
| 16 | Rabbit | 2 | milligrammes. 100 | milligrammes. 50 | 30 secs. | 0.25 | 3½ | Died, 9—17 hrs. |
| 17 | „ | 2 | 20 | 10 | 30 „ | 0.25 | 4 | „ 26 „ |
| 18 | „ | 2 | 20 | 10 | .. | Nil (control) | .. | „ 3 „ |
| 19 | „ | 2½ | 6.875 | 2.5 | 30 „ | „ | 2½ | Recovered. |
| 20 | Cat..... | 1½ | 87.5 | 50 | 30 „ | 0.25 | 3 | „ |
| 21 | „ | 2 | 100 | 50 | 5 mins. | 0.25 | 3½ | Died, over 24 hrs. |
| 22 | „ | 2½ | 125 | 50 | 30 secs. | Nil (control) | 3 | „ 4 „ |
| 23 | „ | 2 | 60 | 30 | 30 „ | 0.25 | 3½ | Recovered. |
| 24 | „ | 1½ | 45 | 30 | 5 mins. | 0.25 | 3½ | „ |
| 25 | „ | 3 | 90 | 30 | 10 „ | 0.25 | 1½ | „ |
| 26 | „ | 2 | 60 | 30 | 30 secs. | Nil (control) | 3 | Died, 4½ hrs. |
| 27 | „ | 2 | 20 | 10 | 30 „ | 0.25 | 4 | Recovered. |
| 28 | „ | 3 | 30 | 10 | 30 „ | Nil (control) | 3 | Died, 30—40 hrs. |

snggest the hope that the method of treatment here advocated may produce good results even when it is not put into operation until considerably longer periods than in any of the above experiments, especially when only slightly *supra-minimal* lethal doses have been received into the tissues.

Conclusions.

Further experiments will be necessary to ascertain the exact limits of the value of this form of treatment, and they will be undertaken immediately by one of us (Rogers) in India, fresh venoms being tried, as it is possible that they may be more rapidly absorbed than those which have been dried and redissolved. We think, however, that the results reported in this communication are sufficiently promising to make it advisable to place them on record, with a view to a trial being given to the method in suitable cases, especially as the crystals of permanganate of potash are actively antiseptic without acting as more than a superficial escharotic, so that the treatment has no markedly injurious effect which can be weighed for an instant against the terrible results of bites by venomous snakes. The process here recommended has already yielded experimental results far in advance of anything hitherto attained.

It is worthy of note that the earlier experiments of the first two authors were stopped nearly 30 years ago by the passing of the Act for regulating experiments on animals in England, but for which this logical sequence of their earlier work might very probably have been made many years ago.

